Programmable and on-demand drug release using electrical stimulation

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(Received 16 December 2014; accepted 2 February 2015; published online 19 March 2015)

Recent advancement in microfabrication has enabled the implementation of implantable drug delivery devices with precise drug administration and fast release rates at specific locations. This article presents a membrane-based drug delivery device, which can be electrically stimulated to release drugs on demand with a fast release rate. Hydrogels with ionic model drugs are sealed in a cylindrical reservoir with a separation membrane. Electrokinetic forces are then utilized to drive ionic drug molecules from the hydrogels into surrounding bulk solutions. The drug release profiles of a model drug show that release rates from the device can be electrically controlled by adjusting the stimulated voltage. When a square voltage wave is applied, the device can be quickly switched between on and off to achieve pulsatile release. The drug dose released is then determined by the duration and amplitude of the applied voltages. In addition, successive on/off cycles can be programmed in the voltage waveforms to generate consistent and repeatable drug release pulses for on-demand drug delivery. © *2015 AIP Publishing LLC*.
[http://dx.doi.org/10.1063/1.4915607]

I. INTRODUCTION

Recent development in drug release devices has shown the capability in delivering accurate amount of drugs at a specific location. Various types of drug release devices, such as hydrogel,[1,2] nano-particles,[3,4] and membrane-based reservoir devices,[5–8] have been extensively studied in literature. Among them, pulsatile drug delivery systems (PDDS) have drawn attention as they allow repeatable and reliable drug release flux for clinical needs. Further, external stimulation signals such as temperature variation,[9,10] magnetic fields,[11–14] and electric fields,[15–21] can be used in PDDS to trigger or control drug release rates, thereby allowing remote control of local drug administration. Most of the PDDS devices are composed of a drug-loading container covered with a functional membrane, with drug release rates through the functional membrane controlled by modulating the external stimulations. For example, Okano *et al.*[9] embedded a temperature-responsive hydrogel in the separation membranes within a PDDS to produce a temperature-dependent permeability for drug molecules, thereby allowing release rates to be responsive to environmental temperature changes. Hoare *et al.*[6,7] assembled a membrane-based device and remotely applied an oscillating magnetic field to heat up the composite membrane. The membrane becomes more permeable to drug molecules at a higher temperature. Thus, one can modulate the drug release rates by programming the magnetic stimulations to achieve a remote pulsatile drug delivery on demand. Alternatively, Cai *et al.*[5] applied magnetic forces to move magnetic particles to block or unblock the pores in a separation membrane, thereby creating a magnetic on/off valve for drug release. These examples show the feasibility and potential of applying external stimuli to control drug release rate with membrane-based PDDS.

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Among these PDDS devices, the ones that can be stimulated and controlled by electrical signals have shown advantages in rapid responses with remote controls for local treatments. Santini *et al.*[22] first used an electrical pulse to burn out a metal thin film over a drug reservoir. Drugs are then released into bulk solution by convective diffusion. Multiple drug release pulses can then be delivered by an array of sealed reservoirs. To enhance the drug release rate, Chung *et al.*[19] modified Santini's design by adding electrodes in the micro-reservoir to create bubbles electrochemically. The bubbles help to mechanically expel the drugs and significantly enhance the release rates. However, both Santini and Chung's micro-reservoir devices are destroyed after use. To amend the problem, Schmidt *et al.*[20] recently fabricated a nanofluidic membrane system then utilized electrokinetic nature of drug molecules to control the magnitude of release rates. These studies show that drug release modulation with electrical stimulations is feasible and can behave in a consistent and repeatable manner.

Although many electrically driven devices have been reported previously, some challenges still remain for a perfect drug release device. The previous PDDSs have regular low drug loadings ($<1\,\mu$L), which keep the PDDSs from long-term usage. Moreover, most PDDSs are designed with a destructive release mechanism, and thus are unable to release multiple times or to control release dosage over a period of time with programmable pulses. This article presents an electrically driven drug release device.

Hydrogels containing ionic drugs were sealed in a cylindrical reservoir of 42 μl with a separation membrane. Screen-printed carbon-paste electrodes across the reservoir were used to develop an electric field inside the drug container, which allowed the electrophoretic forces to drive the drug molecules. An ionic drug, methylene blue (MB), was used to demonstrate the capability of this device. With the help of electric forces, the permeation of ionic molecules through the membrane was accelerated and controlled by adjusting the applied electric field strength. With a square voltage wave, pulsatile drug release was achieved within minutes. Multiple drug pulses were also released by applying a sequence of square voltage waves for on-demand drug release. This electrical drug discharge method was applied to clinical drugs, such as fluorescein isothiocyanate labeled dextran (FITC-dextran), for the realization of programmable drug delivery.

II. MATERIALS AND METHODS

Phosphate buffer solution (pH = 7.2), MB powder, and FITC-dextran (40 kDa molecular weight) were acquired from Sigma-Aldrich, USA. Xanthan gum powder, toluene, and polyethylene (PE) wax were acquired from First Chemical Co., Taiwan. Wax paper was prepared by heating 1 g of PE wax on a 5 × 5 cm piece of regular printing paper (Chung Haw Pulp Co., Taiwan) with a hot plate at 80 °C. Mixed cellulose ester (MCE) membrane with 3 μm pore size was purchased from Advantec, Japan. Carbon paste was acquired from Acheson Co., Malaysia. Poly ethylene vinyl acetate (EVA) was acquired from KingTaipei Co., Taiwan. Blank hydrogel was prepared by mixing 2 wt. % xanthan gum powder with phosphate buffer solution (pH = 7.2) at room temperature. Eight milligram methyl blue powder was then dissolved in 10 ml blank xanthan gum solution as the ionic drug for the drug release test. A similar approach was applied to prepare FITC-dextran gel as the clinical drug.

A. Device fabrication and assembly

The electro-stimulated membrane-based drug delivery device was composed of a top electrode, separation membrane, drug reservoir, and a bottom electrode (Fig. 1). First, a drug reservoir with a small pin hole of 500 μm in diameter was made by compressing hot EVA melt on an aluminum mask (see supplementary material).[25] The main body of the reservoir is a hollow cylinder of 3 mm in diameter and 1.5 mm in height. A piece of 2 × 2 mm membrane was placed above the pin hole and bonded to the reservoir thermally. All of the devices were sealed by MCE membranes in the following sections, with the exception of those in Sec. III for membrane comparison. Then, a top electrode was screen-printed on the EVA reservoir surface with carbon paste. Next, 42 μl of drug-containing gel was loaded in the reservoir. An EVA slab with

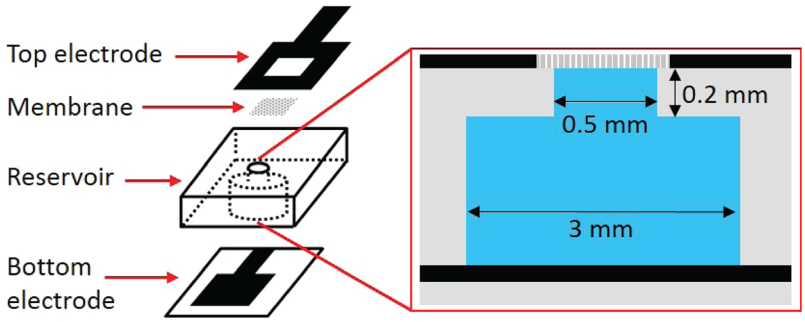

FIG. 1. Exploded view of the drug delivery device.

screen-printed bottom electrode was sealed under the reservoir with EVA melt. Finally, electric wires were used to connect the electrodes to a DC voltage source for the drug release test.

B. Drug release test

The device was submerged in 2 ml fresh phosphate buffered saline (PBS) solution in a glass vial. All the drug release experiments were conducted in a water bath at a constant temperature of 37 °C for at least five repetitions. Constant DC voltage or voltage waveforms were applied to the drug device with a DC power supply (CT30V10A, Chern-Taih, Taiwan). After certain time intervals (10–60 min), the PBS solution was replaced with a fresh batch, and the drug concentration in the old PBS batch was measured by a UV-Vis spectrometer (V-670, Jasco, Inc., USA). Each experiment was repeated at least five times to check the repeatability of the drug release devices. The MB and FITC-dextran concentrations were determined by the absorption peaks at 663 and 492 nm, respectively.[25]

III. RESULTS AND DISCUSSION

A. Electrophoretic release mechanism

The release mechanism from our proposed device involved electric-field-driven movement of charged molecules with the principle of operation shown schematically in Fig. 2(a). Without any applied voltage, a fairly small amount of MB was released from the device due to the concentration difference between the drug-containing hydrogel and bulk solution. As a DC voltage was applied on the device, an electric field developed between the top and bottom electrodes. With the help of electric forces, as shown by Chung *et al.*,[17] ionic molecules pushed through the membrane and diffused into the bulk solution. To demonstrate the electrophoretic mechanism, a device containing MB was immersed in water (Fig. 2(b)). Without any applied voltage, the MCE membrane turned blue after 20 min with MB slowly being released into the surrounding fluids based on the concentration difference in the hydrogel and surrounding fluid. When a positive bias voltage was applied at the bottom electrode, the electric field drove the cationic MB molecules, moving towards the top electrode (ground). MB molecules quickly migrated across the porous structure of the membrane according to the electric fields and diffused into the external bulk solution. A strong release flux from the device was observed within 5 min. The fast responses in drug release rates with the electric stimulus not only showed the feasibility of electrical drug release control but also the possibility of initiating and controlling pulsatile drug release.

B. Relationship between applied voltage and release rates

Fig. 3 showed the released MB from the device when a DC voltage was applied for 8 h. Without electrical stimulus, the concentration difference between the hydrogel and the surrounding PBS solution slowly released MB from the device. The released amount was almost

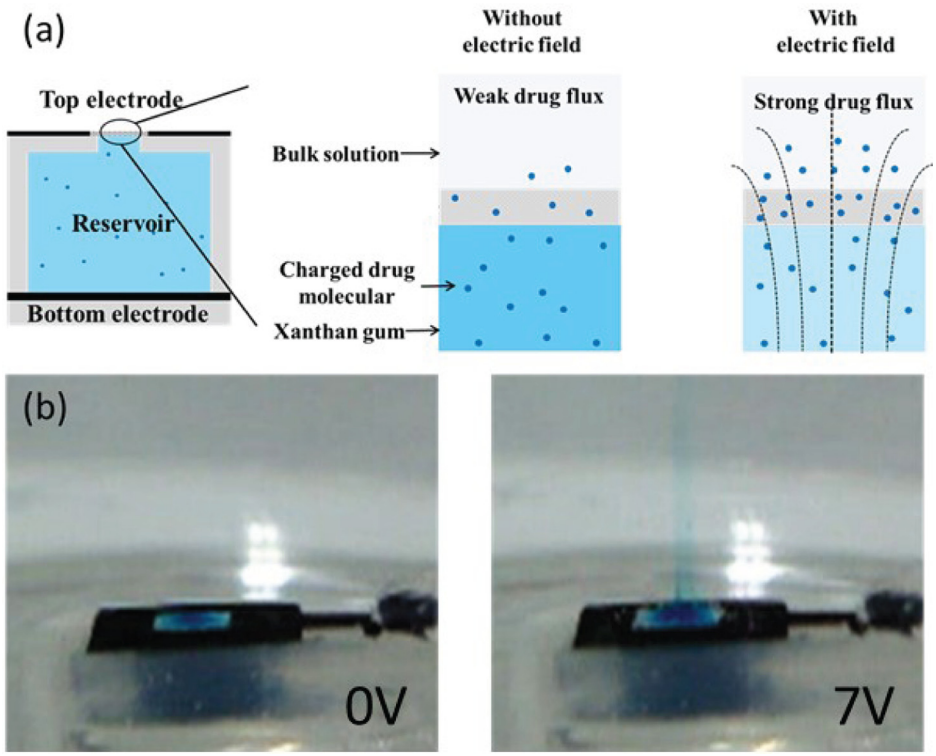

FIG. 2. (a) Schematic diagrams of the drug release mechanism from the device. (b) Submerged devices in PBS solutions: devices sealed by MCE membrane without voltage applied (right) and with an applied voltage of 7 V for 20 min (right). A stream of methylene blue (right) can be clearly observed, indicating a much faster drug release rate as compared to the device with the pure diffusion.

proportional to the duration of the applied voltage at a steady release rate of 0.1 μg/h. For solute diffusion through a membrane into an infinite medium, the release rate could be described by the following equation:[23]

$$\frac{M_t}{A} = \frac{DC_1}{l}\left(\mathrm{t} - \frac{l^2}{6D}\right), \tag{1}$$

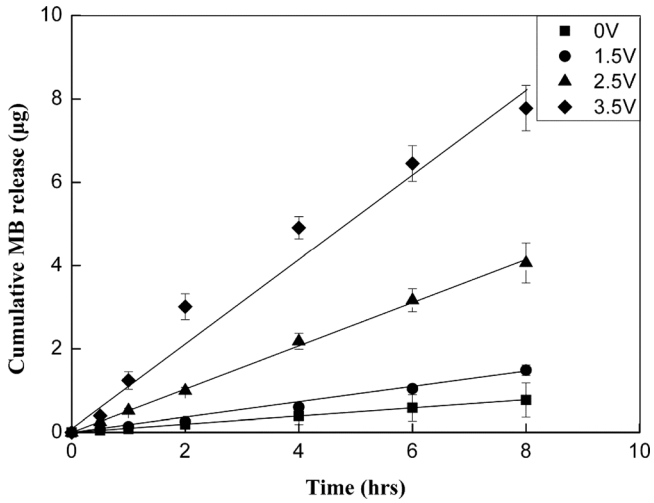

FIG. 3. Cumulative amount of methylene blue released into the surrounding solution at various applied voltages. The error bars indicate the standard deviations.

where M_t is the accumulated release amount of the drug molecules; A is the area of membrane; D is the diffusivity of drug molecules in the membrane; C_1 is the concentration difference across the membrane; t is the duration of the applied voltage; and l is the thickness of the membrane. From Eq. (1), the diffusivity of MB in this system without applied voltage was estimated to be 6.83×10^{-8} cm^2/s—the same order of magnitude for small molecules in water. Since the thickness of the membrane was only 120 μm, the induction period in Eq. (1), $l^2/6D = 350$ s, was quite small compared to the overall release process. Hence, the last term in Eq. (1) can be neglected with the released amount being linear to time, as observed in the experiment.

The electrophoretic motion of MB molecules increased with the help of applied electric field and facilitates the release rate through the membrane. Similar to the pure membrane diffusion problem without electrical stimulus, the release amounts under electrical stimulation were proportional to the duration of the applied voltage (Fig. 3), indicating that the mass transfer resistance was mainly from the molecular permeation in membrane. At a higher applied voltage, stronger electric fields led to a larger MB electrophoretic motion, resulting in a steeper slope in transient MB release profile. The slope, or the release rate, jumped from 0.19 μg/h at 1.5 V to 0.97 μg/h at 3.5 V. These release rates were roughly of the same order as those reported by Fine *et al.*,[21] but with a slightly higher voltage. The transient MB release profiles can be described by Eq. (1), with the effective diffusivity D_{eff} summarized in Table I. The higher value of D_{eff} at a higher applied voltage showed that the drug permeated through the membrane faster in a stronger electric field. The response time to the electrical stimulation was then estimated by the facilitated permeation time scale as l^2/D_{eff}, ~4 min at 3.5 V. Due to this acceleration by applied electric fields, drug release rates could be adjusted by tuning the applied voltage waveforms, thereby achieving a pulsatile drug release, as provided in Secs. III C and III D.

C. Pulsatile drug release

Fig. 4 illustrates pulsatile release of MB by applying a square voltage wave. Initially, to reduce the diffusional drug release, a negative voltage (−3.5 V) was applied on the bottom electrode to hold the positively charged MB molecules. In the bulk solution, no MB was observed with the color of the membrane remaining unchanged (white) when the negative voltage was continuously applied. Once the voltage switched to +3.5 V, MB started to release with a blue spot on the membrane observed, indicating MB permeation through the membrane. MB was detected in the bulk solution from UV spectra with absorbance increasing over time. Twenty minutes after applying the +3.5 V, the absorbance reached a plateau and remained constant over the next 20 min. This plateau indicated saturation of MB inside the membrane, or a local depletion of MB in the reservoir near the bottom electrode, with a slow but steady release rate expected. The time scale of this PDDS for actively transporting drugs was about 20 min. These results were close to those found in Refs. 21 and 22, but longer than those found in Ref. 19, which used a membrane destruction mechanism for quick drug release. To shut off the drug release, the voltage at the bottom plate was switched to −3.5 V again at t = 59 min. The release rate dropped down quickly to a low level within 5 min, with a small release rate; possibly due to the diffusion of residual MB in the membrane. The response in drug release rates to electrical stimuli were fast enough that the absorbance profile was nearly presented as a square wave

TABLE I. Continuous release rate as a function of applied voltage.

Applied voltage (V)	Continuous release rate (μg/h)	Apparent diffusivity (10^{-7} cm^2/s)
0.0	0.10 ± 0.05	0.68
1.5	0.19 ± 0.02	1.24
2.5	0.51 ± 0.06	3.66
3.5	0.97 ± 0.07	7.64

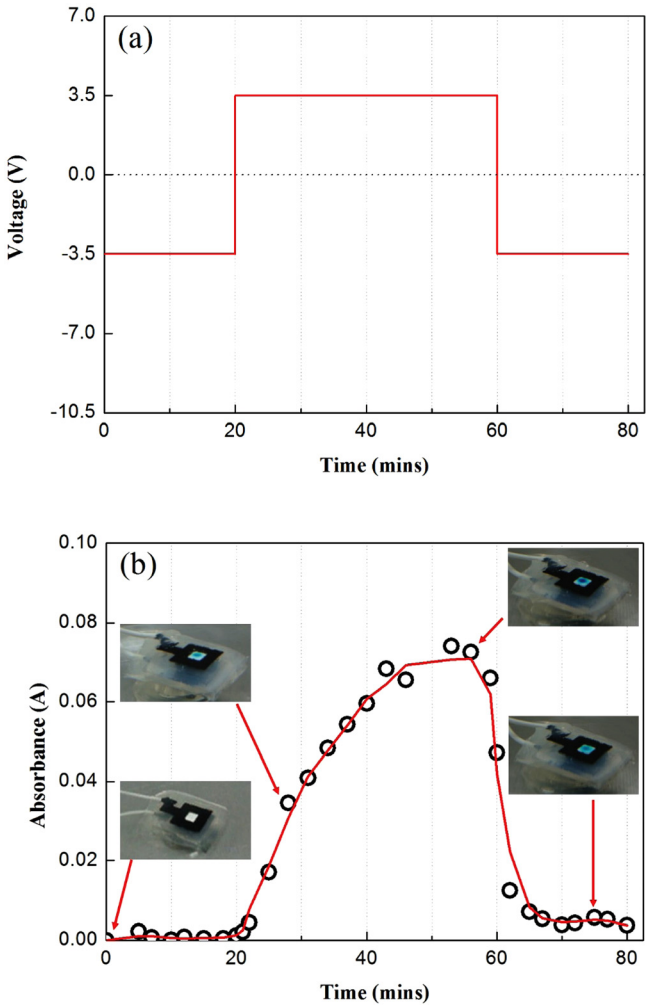

FIG. 4. (a) The applied voltage waveform for pulsatile drug release. (b) The response in absorbance of bulk solution at 663 nm. The inset pictures show the color transition of the separation membrane at different times as pointed out by the arrows.

as compared to the applied voltage. As a result, the applied voltage waveform could be further modulated to program drug release rates from the device.

D. Programmable drug release

Multiple square waves (Fig. 5(a)) are used to test the device performance on sequentially pulsatile drug release. Each pulse cycle contains two modes: "on" and "off" states. When in an "on" state, the device releases MB by applying a positive voltage at the bottom electrode. The drug molecules are expelled by the bottom electrode and move towards the bulk solution. Hence, large amount of drugs are released quickly. Alternatively, when the device is in an "off" state, a negative voltage is applied. MB molecules are mobilized towards the bottom electrode with the device releasing little or no drug. The release rates at individual cycles are summarized in Fig. 5(b). When the applied voltage is 1.5 V, the difference in release rates between the on and off states is small, with an on/off ratio of 2 (Table II). From the release experiments at constant voltage, the difference in apparent diffusivity is about twice as large as that of the pure diffusion. Therefore, the release rates at on/off modes are of the same order. As the applied voltage increases, the apparent diffusivity increases. The on/off ratio can increase up to 8 when a 3.5 V DC voltage is applied. The drug release can be easily triggered by applying voltage waveforms repetitively, as shown by Santini *et al.*,[22] but with a longer release time. Moreover,

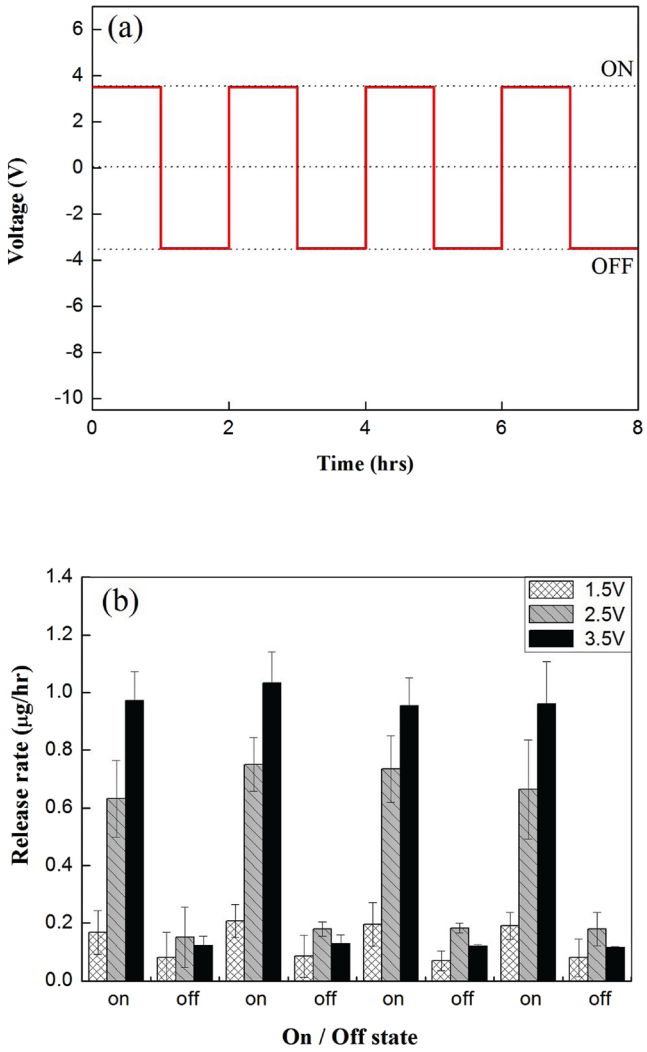

FIG. 5. (a) The waveform for sequential pulsatile drug release: each on/off cycle contains a positive voltage to turn on the pulsatile release and a negative voltage to turn off the release rate. (b) Release rates of MB (cationic model drug molecules) over four successive on/off cycles at various applied voltages.

one can also apply the release pulses at different timings,[25] and can observe consistent responses in drug release rates following the electric field strength.

E. Polarization of nonionic drugs

In the practical application, drug molecules were roughly classified according to their electrical properties: cationic, anionic, and nonionic drugs.[24] Our proposed electrophoretic devices were effective in electrically controlling the dry release of cationic and anionic molecular drugs. Ionic drug labels or ionic drug carriers could be adapted as a vehicle for carrying nonionic

TABLE II. Release rates and on/off ratio as a function of applied voltages for pulsatile drug release.

Applied voltage (V)	On rate (μg/h)	Off rate (μg/h)	On/off ratio
1.5	0.19 ± 0.06	0.08 ± 0.06	2.43
2.5	0.70 ± 0.12	0.17 ± 0.05	4.01
3.5	0.98 ± 0.10	0.12 ± 0.02	8.11

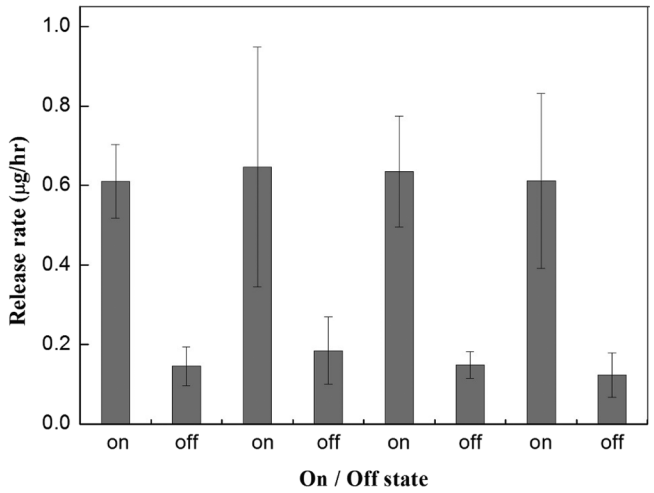

FIG. 6. The release rate of FITC-dextran over four successive on/off cycles (1 h) of the external electric field (3.5 V).

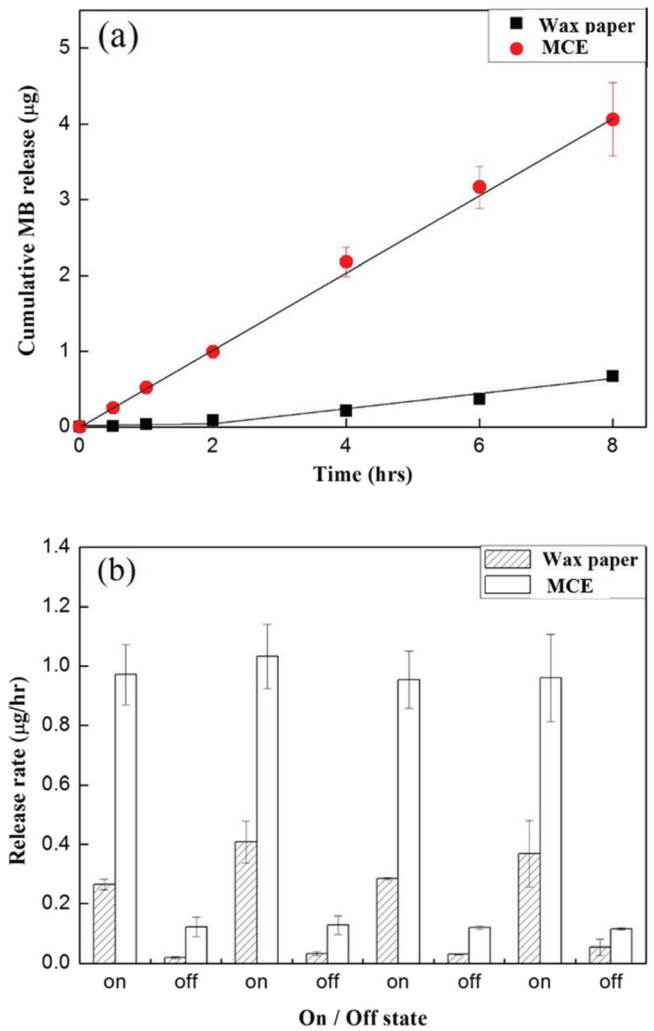

FIG. 7. Comparison of release rates from devices with wax paper and MCE as the membrane. (a) Accumulated amount of methyl blue released into the surrounding solution at 2.5 V with wax paper and MCE membranes. (b) Release rates of MB over four successive on/off cycles of the external electric field. The applied voltage wave is the same as that in Fig. 5(a).

TABLE III. Comparison between the PDDS sealed with various membranes.

Membrane types	Pulsatile release[a] (μg/h)	On/off ratio
MCE	0.98 ± 0.10	8.11
Wax paper	0.33 ± 0.07	9.70

[a]At 3.5 V applied voltage.

drugs for electrophoretic control release in our device. For instance, dextran (40 kDa)—a non-ionic drug—is commonly used as an antithrombotic agent in microsurgery. After labelling it with FITC, the overall structure of drug molecules became negatively charged. Hence, FITC-dextran molecules migrated according to external applied electric fields. Similar electric waveforms, as those in MB pulsatile tests, were used in FITC-dextran pulsatile drug release experiments. Since FITC-dextran were negatively charged, the polarity of electric waveforms were opposite of those specified in Fig. 5(a). The drug release experiments were carried out in a water bath at 37 °C. Drug release data were collected for four successive on/off cycles with applied voltage of 3.5 V (Fig. 6). Effective pulsatile drug release rates of 0.63 μg/h were observed. Meanwhile, the flux ratio between the on/off states was 4.24; much smaller than that of MB molecules. As a result of the large molecular weight of dextran and the low ionic valence in FITC, the electric mobility of FITC-dextran was smaller than that of MB; thereby resulting in a smaller apparent diffusivity. Nevertheless, presented data demonstrate the feasibility of applying electrophoretic drug release on non-ionic clinical drug of high molecular weight by ionic labeling.

F. Selection of membranes

Selection of the separation membranes can help to modulate drug release rates. Fig. 7 compares the drug release profile from the devices with wax paper and MCE membranes. The release rate through wax papers under a constant applied voltage is 84 ng/h, which is about nine times lower than that from MCE membrane. However, the release amount is still linear to time, indicating that the mass transfer resistance of wax paper dominates the drug release process. The difference in membrane microstructures is the major cause for the mass transfer barrier. MCE membrane is hydrophilic (apparent contact angle $\theta_c = 18°$)[25] and is composed of ordered pore arrays. On the other hand, wax paper is hydrophobic ($\theta_c = 101°$) and is composed of woven fibers with a large tortuosity (Fig. S5(b) in the supplementary material[25]). Thus, it is more difficult for drug molecules to penetrate through wax paper than MCE membrane. The larger mass transfer barrier of wax paper, however, shows on both diffusional and electrokinetic mass flux. Thus, the on/off ratio in pulsatile release process (Fig. 7(b)) is about the same for both wax paper and MCE membrane (Table III).

IV. CONCLUSIONS

An electrically driven drug delivery device was fabricated to actively eject ionic drugs multiple times from a membrane-sealed reservoir of 42 μl into surrounding fluids. MB, a cationic drug, was used as a model drug to test the capability of the fabricated device. The control release process of our proposed device relied on the large mass transfer barrier of the separation membrane. MB permeated through the membrane at a release rate of 0.1 μg/h. When the device was actuated, an electric field was generated and the electrokinetic force increases the mobility of ionic drug molecules, which helps the drug permeation process through the separation membrane. The drug release rate was accurately controlled and increased to 1 μg/h by adjusting externally applied voltages. This electrokinetic approach facilitated the release rates significantly as compared to a regular diffusional release. Thus, pulsatile drug delivery can be achieved by applying external voltages of a square waveform. Further, the device released multiple pulses at specific times using programmed voltage waveforms with an on/off ratio up to 8. A similar approach could be applied on releasing nonionic clinical drugs with ionic labels.

A clinical drug dextran tagged with negatively charged FITC could be electrically discharged from the pulsatile drug delivery device. Due to the large molecular weight, FITC-dextran had less electric mobility, with the on/off ratio being smaller.

Further study on how to electrically mobilize drugs is necessary to increase the drug release rates. Microstructures of the separation membrane are also found to be critical to the drug release phenomena. In summary, this drug delivery device shows the feasibility of applying electrokinetic approach to deliver ionic drugs. By applying specific electric waveforms, one can control not only the drug release rates but also the timing of drug release. The same approach can be further extended to other ionic drugs, such as insulin, micelles, vesicles, and surface charged nanoparticles for the realization of drug release on demand.

ACKNOWLEDGMENTS

The authors thank Ms. T. Kirk for manuscript editing. This research was supported by the Ministry of Science and Technology in Taiwan (MOST 103-2923-E-002-010-MY3).

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